measuring a non-radioactive isotope-labeled CO_2 excreted in the expired air after oral administration.

REMARKS

I. Status of the Claims

Claims 1-4 and 6-19 are pending in the application. Claims 1, 3, 4, and 6-15 have been amended. Claim 5 has been cancelled. Claims 16-19 have been added.

Claims 3, 4, and 6-15 have been amended to more particularly claim that which Applicants consider to be the invention. Claims 7 and 14 have been rewritten as independent claims. Claims 8-13 have been rewritten to ultimately depend from claim 7.

New claim 16 has been added to depend from claim 14, reciting the limitation of amended claim 10. New claim 17 recites a preparation having an oral dosage form. Support for claim 17 can be found in the specification at, for example, p. 13, lines 15-22.

New claim 18 has been added to recite a preparation having at least one additional ingredient selected from pharmaceutically acceptable carriers and additives. Support for this claim can be found in the specification at, for example, p. 13, line 23 to p. 15, line 14, and p. 16, lines 1-6.

New claim 19 has been added to recite a preparation wherein at least one of C and O is labeled with a non-radioactive isotope, and the preparation is designed for measuring a non-radioactive isotope-labeled CO_2 excreted in the expired air after oral administration. Support for this claim can be found in the specification at, for example, p. 12, line 26 to p. 13, line 3.

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No new matter has been added by these amendments or new claims, nor do these amendments or new claims raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Accordingly, Applicants respectfully request examination of claims 1-4 and 6-19.

II. Claim Objections

Claims 5-15 are objected to as being in improper form.

Claim 5 has been cancelled. Claims 6-15 have been amended to remove the multiple dependencies. In view of these amendments, it is believed that the claims comply with 37 C.F.R. § 1.75(c). Accordingly, Applicants respectfully request examination of claims 6-15.

III. Rejection under 35 U.S.C. § 102

el Kouni

Claims 1-4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,670,331 ("*el Kouni*"). *Office Action* at p. 2. Applicants respectfully traverse this rejection in view of the following amendments and remarks.

The Examiner cites *el Kouni* for disclosing "a preparation for determining pyrimidine metabolism comprising a pyrimidine compound in which at least one carbon atom is labeled with an isotope, specifically, ^{14}C-labeled 5-fluorouracil." *Id.* at p. 2.

Claim 1 has been amended to recite a preparation comprising a pyrimidine compound or its metabolite in which at least one of C, O and N is labeled with a non-radioactive isotope. Support for this amendment can be found in the specification at, for example, p. 11, line 26 to p. 12, line 2. Claim 1 as amended further recites that the

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preparation is designed for administration to a subject. Support for this amendment can be found in the specification at, for example, p. 12, line 26 to p. 13, line 2.

In contrast, *el Kouni*'s diagnostic test involves measuring the enzyme activity in a biological sample, such as blood. *el Kouni* at col. 4, lines 61-63. A radioactive-labeled compound, *e.g.*, [2-^{14}C]5-fluorouracil, is added to the blood samples to monitor a cancer patient's tolerance or intolerance to fluoropyrimidine chemotherapeutic agents. *Id.* at col. 1, lines 7-11.

Applicants respectfully submit that *el Kouni* does not anticipate claim 1 as amended. *el Kouni* fails to disclose the use of a non-radioactive agent, as claimed, and does not teach any technique for monitoring non-radioactive by-products resulting from the diagnostic test. Moreover, *el Kouni* describes an *in vitro* assay, where the radioactive labeled compound is added to a biological sample and not to a subject. Thus, by disclosing testing on blood samples, *el Kouni* does not teach a preparation designed for administering to a subject, as claimed.

"For anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly." M.P.E.P. § 706.02(a); *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). Because *el Kouni* does not disclose all of the limitations of amended claim 1, *el Kouni* does not anticipate amended claim 1.

Claims 7 and 14, which were not previously considered by the Examiner, have been rewritten as independent method claims, reciting the steps of administering to the subject a preparation wherein at least one of C, O, and N is labeled with a non-radioactive isotope. Because *el Kouni* does not disclose administering a preparation to

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a subject or the use of a compound labeled with a non-radioactive isotope, as claimed, *el Kouni*, also does not anticipate claims 7 and 14.

Moreover, *el Kouni* teaches away from administering a preparation to a subject because it discloses a radioactive isotope. Thus, *el Kouni* does not render obvious the present claims.

Accordingly, Applicants respectfully request withdrawal of this rejection.

Van Kuilenburg

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clinical Chemistry, Vol. 46, pp. 9-17, 2000 ("*Van Kuilenburg*"). *Office Action* at pp. 2-3. Applicants respectfully traverse this rejection in view of the following amendments and remarks.

The Examiner cites *Van Kuilenburg* for disclosing a preparation such as ^{14}C-labeled thymine. *Id.* at p. 2. The Examiner asserts that because *Van Kuilenburg*'s preparation has "the same active ingredient as claimed ... [it] must inherently have the same functional properties." *Id.* at p. 3.

As discussed above, claim 1 has been amended to recite a pyrimidine compound or its metabolite in which at least one of C, O and N is labeled with a non-radioactive isotope. Moreover, claim 1 has been amended to define a preparation designed for administration to a subject.

Van Kuilenburg describes an assay to identify patients suffering from complete or partial dihydropyrimidine dehydrogenase deficiency. *Van Kuilenburg* at p. 9. *Van Kuilenburg*'s assay is an *in vitro* assay where the dihydropyrimidine dehydrogenase

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activity of samples obtained from human subjects, such as fibroblasts, leukocytes, and human liver, was monitored in a reaction mixture containing radioactive-labeled [4-^{14}C]thymine. *Id.* at p. 11. Thus, *Van Kuilenburg*'s preparation is combined with a blood or tissue sample and is not administered to a subject. Because *Van Kuilenburg* fails to disclose the use of a non-radioactive labeled compound, or a preparation designed for administration to a subject, as claimed, *Van Kuilenburg* does not anticipate claims 1-4.

Claims 7 and 14, which were not previously considered by the Examiner, have been rewritten as independent method claims, reciting the steps of administering to the subject a preparation wherein at least one of C, O, and N is labeled with a non-radioactive isotope. Because *Van Kuilenburg* does not disclose administering a preparation to a subject or the use of a non-radioactive labeled compound, as claimed, *Van Kuilenburg*, does not anticipate claims 7 and 14.

Moreover, *Van Kuilenburg* teaches away from administering a preparation to a subject because it discloses a radioactive isotope. Thus, *Van Kuilenburg* does not render obvious the present claims.

Accordingly, Applicants respectfully request withdrawal of this rejection.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX

(Version with Markings to Show Changes Made)

1. (Amended) A preparation for determining pyrimidine metabolizing activity, comprising as an active ingredient a pyrimidine compound or its metabolite in which at least one of C, O and N is labeled with **[~~an~~]** **a non-radioactive** isotope**, the preparation being designed for administering to a subject**.

3. (Amended) A preparation according to claim 2, wherein the pyrimidine metabolizing enzyme is at least one member selected from **[~~the group consisting of~~]** dihydropyrimidine dehydrogenase, dihydropyrimidinase and ß-ureidopropionase.

4. (Amended) A preparation according to **[~~any one of claims~~]** **claim** 1 **[~~to 3~~]**, wherein the pyrimidine compound or its metabolite is at least one member selected from **[~~the group consisting of~~]** 5-fluorouracil, uracil, thymine, 5-fluorodihydrouracil, dihydrouracil, dihydrothymine, fluoro-β-ureidopropionic acid, β-ureidopropionic acid, β-ureidoisobutyric acid, doxifluridine, tegafur and carmofur.

6. (Amended) A preparation according to **[~~any one of claims~~]** **claim** 1 **[~~to 5~~]**, wherein the **non-radioactive** isotope is at least one member selected from **[~~the group consisting of~~]** ^{13}C, **[~~^{14}C,~~]** ^{18}O and ^{15}N.

7. (Amended) A method for determining pyrimidine metabolizing activity in an individual subject, comprising:

administering **to the subject** a preparation **[~~according to any one of claims 1 to 6 to the subject,~~]** **comprising a pyrimidine compound or its metabolite wherein at least one of C, O, and N is labeled with a non-radioactive isotope;** and

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measuring [~~behavior of an~~] **a non-radioactive** isotope-labeled metabolite.

8. (Amended) A method [~~for determining pyrimidine metabolizing activity in an individual subject, comprising administering a preparation according to any one of claims 1 to 6 to the subject, and measuring excretion behavior of an~~] **according to claim 7, wherein the measuring comprises measuring the non-radioactive** isotope-labeled metabolite excreted from the body.

9. (Amended) A method [~~for determining pyrimidine metabolizing activity in an individual subject, comprising administering a preparation according to any one of claims 1 to 6 to the subject, and measuring behavior of~~] **according to claim 8, wherein the non-radioactive isotope-labeled metabolite is isotope-labeled CO_2, and the measuring comprises measuring the** isotope-labeled CO_2 excreted in the expired air.

10. (Amended) A method according to claim 7 [~~or 8~~], wherein the pyrimidine metabolizing activity to be determined is an activity of at least one pyrimidine metabolizing enzyme selected from [~~the group consisting of~~] dihydropyrimidine dehydrogenase, dihydropyrimidinase and β-ureidopropionase.

11. (Amended) A method [~~for assessing pyrimidine metabolizing activity in an individual subject, comprising administering a preparation according to any one of claims 1 to 6 to the subject, and measuring behavior of an isotope-labeled metabolite, and comparing the behavior in the subject with behavior in~~] **according to claim 7, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject is compared with the measurement from** a healthy subject.

12. (Amended) A method [~~for assessing pyrimidine metabolizing activity in an individual subject, comprising administering a preparation according any one of~~

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~~claims 1 to 6 to the subject, measuring excretion behavior of an isotope-labeled metabolite excreted from the body, and comparing the excretion behavior in the subject with excretion behavior in~~] **according to claim 8, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject is compared with the measurement from** a healthy subject.

13. (Amended) A method [~~for assessing pyrimidine metabolizing activity in an individual subject, comprising administering a preparation according to any one of claims 1 to 6 to the subject, measuring excretion behavior of isotope-labeled CO_2 excreted in the expired air, and comparing the CO_2 excretion behavior in the subject with CO_2 excretion behavior in~~] **according to claim 9, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject is compared with the measurement from** a healthy subject.

14. (Amended) A method for establishing a dosage regimen of a pyrimidine drug for an individual subject, comprising:

administering to the subject a preparation comprising a pyrimidine compound or its metabolite wherein at least one of C, O, and N is labeled with a non-radioactive isotope;

[~~assessing~~] **measuring a non-radioactive isotope-labeled metabolite to assess** pyrimidine metabolizing activity in the subject [~~by the method according to claim 10 or 11 before administration of the drug,~~] ; and

determining the dosage regimen based on the **assessed** pyrimidine metabolizing activity.

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15. (Amended) A method according to claim 14, wherein the pyrimidine drug is a fluorouracil drug selected from [~~the group consisting of~~] 5-fluorouracil, tegafur, carmofur and doxifluridine.

16. (New) The method according to claim 14, wherein the pyrimidine metabolizing activity to be determined is an activity of at least one pyrimidine metabolizing enzyme selected from dihydropyrimidine dehydrogenase, dihydropyrimidinase and ß-ureidopropionase.

17. (New) The preparation according to claim 1, wherein the preparation has an oral dosage form.

18. (New) The preparation according to claim 1, further comprising at least one additional ingredient selected from pharmaceutically acceptable carriers and additives.

19. (New) The preparation according to claim 17, wherein at least one of C and O is labeled with a non-radioactive isotope, and the preparation is designed for measuring a non-radioactive isotope-labeled CO_2 excreted in the expired air after oral administration.

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